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Brief Report

Pyridostigmine Used as a Nerve Agent Pretreatment Under Wartime Conditions

LTC Jill R. Keeler, AN; COL Charles G. Hurst, MC; COL Michael A. Dunn, MC

Objective.—To determine the adverse effects of pretreatment with pyridostigmine bromide for nerve agent exposure during wartime.

Design.—A retrospective study.

Setting.—Southwest Asia.

Participants.—Personnel who provided medical support to the XVIII Airborne Corps. These medical officers supplied information pertaining to symptoms and disposition of 41 650 soldiers who received pyridostigmine at the onset of hostilities of Operation Desert Storm.

Intervention.—Pyridostigmine bromide, 30 mg orally, was self-administered every 8 hours while under the threat of nerve agent attack (for 1 to 7 days).

Main Outcome Measure.—Physiologic changes attributable to pyridostigmine that resulted in need for medical attention, discontinuation of the drug, hospitalization, and/or evacuation from Southwest Asia.

Results.—About half of the population noted physiologic changes that were not incapacitating, such as increased flatus, abdominal cramps, soft stools, and urinary urgency. Approximately 1% of the soldiers believed they had effects that warranted medical attention, but fewer than 0.1% had effects sufficient to discontinue the drug. Nonincapacitating symptoms often occurred; however, military mission performance was not impaired.

Conclusion.—While under the threat of nerve agent attack, pyridostigmine can be administered to virtually all soldiers.

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DURING Operation Desert Storm there was a credible threat of chemical warfare even though there was never actual use of chemical agents. Intelligence reports indicated that the Iraqi chemical arsenal contained nerve, vesicant, and blood agents. Nerve agents are organophosphorus inhibitors of acetylcholinesterase, such as sarin and tabun. The vesicants are skin-blistering compounds, such as mustards and arsenicals, while blood agents are the cyanides, inhibitors of cytochrome oxidase.

The US Armed Forces' approach to the medical management of actual or anticipated nerve agent injuries employs a regimen that consists of pretreatment with pyridostigmine bromide tablets prior to nerve agent exposure, followed by atropine citrate and pralidoxime chloride by autoinjector intramuscularly on actual exposure.[1] Proper administration of this drug combination provides significantly increased survival after lethal exposures to nerve agents above that provided by atropine and pralidoxime therapy alone.[2]

The recent addition of pyridostigmine to the US therapeutic regimen for nerve agent poisoning was based on efficacy data in animals[3] and safety studies in humans.[4-8] Operation Desert Storm necessitated the first large-scale human use of pyridostigmine under field conditions prior to anticipated nerve agent attack. The Food and Drug Administration issued an interim rule, effective December 21, 1990, that obtaining informed consent was not feasible for wartime use of pyridostigmine in Operation Desert Storm.[9]

The troops were given pyridostigmine in a blister pack containing twenty-one 30-mg pyridostigmine bromide tablets. The decision to begin, continue, or discontinue pyridostigmine rested with each major unit commander, based on his chemical, medical, and intelligence staff officers' advice. Troops took one to 21 pyridostigmine tablets at the specified regimen of one tablet every 8 hours.

At the prescribed dosage of pyridostigmine, anticipated undesirable effects were a slight increase in flatus, occasional diarrhea, and a decrease in heart rate of about five beats per minute.[8] Cases of nausea, headache, and vivid daydreams have also been reported.[6] Data were collected in Saudi Arabia to determine whether the physiologic responses to pyridostigmine were the same under the conditions of anticipated chemical attack as had been noted under controlled, non–combat-associated conditions.

From the US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

Reprint requests to Commander, US Army Medical Research Institute of Chemical Defense, ATTN: SGRD-UV-YY/LTC Keeler, Aberdeen Proving Ground, MD 21010-5425.

Effects of Pyridostigmine Pretreatment*

Effect	Range of Incidence, %
Gastrointestinal symptoms	≥50
Urinary urgency and frequency	5-30
Headaches, rhinorrhea, diaphoresis, tingling of extremities	<5
Need for medical visit	1
Discontinuation on medical advice	<0.1

*Based on reports from medical personnel providing care to 41 650 soldiers (6.5% women) who took pyridostigmine bromide orally at 30 mg every 8 hours for periods of 1 to 7 days. Drug administration resulted in 483 clinic visits, and use of the drug was discontinued in 28 soldiers.

Methods and Results

The XVIII Airborne Corps instructed 41 650 soldiers (6.5% women) to take pyridostigmine tablets at the onset of Operation Desert Storm hostilities in January 1991. The dosage of pyridostigmine, prescribed as one tablet every 8 hours, was variable depending on the order issued by each unit commander; total dosage ranged from one to 21 tablets over 1 to 7 days, with 34 000 soldiers reportedly taking the medication for 6 to 7 days. In all, 234 000 person-days of pyridostigmine administration occurred. Total dosages differed among the six major units of the corps. In some instances, depending on commanders' assessment of the nerve agent threat, the regimen was stopped and restarted repeatedly. Few soldiers admitted to discontinuing pyridostigmine without medical advice. Although it is likely that some individuals discontinued the drug, actual data were not obtainable.

We queried approximately 30 medical officers (physicians and physician's assistants) as to the number of aid station or clinic visits, discontinuations, hospitalizations, and evacuations attributable to pyridostigmine. These officers were in close daily contact with the combat units they served. They included the division surgeons who had responsibility for all medical care, hospitalization, and evacuation of soldiers in this corps. They also provided us with their impressions of the incidence of general physiologic response to pyridostigmine and potential adverse effects.

Effects of pyridostigmine pretreatment experienced by the soldiers are shown in the Table. Regardless of the total dosage or pattern of pyridostigmine administration, gastrointestinal changes, including flatus, loose stools, abdominal cramps, and nausea, were noted by about half the troops. Other reported effects were urinary urgency, headaches, rhinorrhea, diaphoresis, and tingling of the extremities. These effects were considered tolerable. They did not noticeably interfere with performance of the full range of demanding physical and mental tasks required of these soldiers.

Intolerance to pyridostigmine was defined as a perceived need for medical attention. A total of 483 aid station or clinic visits were related to pyridostigmine administration. Specific information as to when symptoms occurred in relation to dosing was not obtained at every visit. The general impression was that the symptoms were experienced within hours after taking the first tablet. In some individuals these symptoms continued as long as pyridostigmine was taken, and in others they abated after 1 or 2 days of use. Gastrointestinal disturbances severe enough to prompt medical attention accounted for 313 of these visits. Another 150 soldiers had frequency or urgency of urination. Five complained of bad dreams, three of worsening of acute bronchitis, and three of headache. Three had slurred speech (one of these also complained of "blurry" vision) but had normal findings on neurological examinations. Rashes occurred in two individuals, one of whom also had edema and urticaria of his hands and feet that responded to diphenhydramine hydrochloride. One soldier complained of vertigo; a soldier with a history of asthma had bronchospasm that was temporally associated with pyridostigmine administration.

An unexpected adverse association was seen in two otherwise normotensive individuals, who experienced acute elevations in blood pressure (180 to 220/110 to 120 mm Hg) and sought medical aid because of bleeding. One individual had epistaxis. The second bled profusely from a shaving nick. He discontinued pyridostigmine for 2 days with resolution of hypertension. When he restarted the drug, not being positive of its association with his symptoms, significant hypertension promptly recurred. He had a normal complete blood cell count, prothrombin time, partial thromboplastin time, platelet count, and bleeding time.

Pyridostigmine therapy was discontinued by the unit physician for 28 soldiers: the three with exacerbated acute bronchitis, the asthmatic, the two with allergic reactions, the two hypertensive patients, and 20 soldiers with intolerable nausea and diarrhea. One physician discontinued his own therapy because of gastrointestinal effects and headaches.

There were no medical evacuations among this corps because of problems with pyridostigmine.

One medical specialist took two pyridostigmine tablets simultaneously in an effort to make up for a missed dose. After realizing he was experiencing a mild cholinergic crisis, he self-administered atropine by autoinjector intramuscularly and reported to his medical treatment facility; he was admitted for observation, and reportedly had no further effects.

Additional information was volunteered by hospital personnel who took pyridostigmine during the third week of January or last week of February 1991. In general, they noted the same gastrointestinal and urinary disturbances described above. Several physicians admitted to discontinuing pyridostigmine because of the unpleasant effects. Two women, with body weights of approximately 45 to 50 kg, recounted that their experience with pyridostigmine included increased salivation, severe abdominal cramps, nausea, diaphoresis, and muscular twitching. Unfortunately, our retrospective study did not provide data relating symptoms to body size or gender, a point worthy of further investigation.

Comment

Soldiers taking pyridostigmine under combat conditions performed at full effectiveness but had a higher incidence of minor intestinal and urinary symptoms than expected. Because of the nerve agent threat, there was no control or placebo-treated population of soldiers not taking pyridostigmine and subject to identical combat stresses. Clearly, the other stress factors present in this combat situation could have contributed to these symptoms; therefore, our data represent a worst-case estimate of effects attributable to pyridostigmine. Our retrospective gathering of anecdotal information from unit medical officers within 10 days of the use of pyridostigmine may have missed minor events; however, the nature of the field medical system provided assurance that all events that required evacuation, referral, or hospitalization were recorded.

Soldiers may not have thought that their symptoms warranted a clinic visit, may have become accustomed to the perceived changes, or may have developed a pharmacologic tolerance to pyridostigmine. Some reported that when pyridostigmine was taken with a meal, gastrointestinal complaints decreased. Practices such as this were implemented by some units to decrease the incidence of symptoms and enhance compliance. Indeed, full compliance with an every-8-hour regimen would be unlikely when soldiers themselves believed the nerve agent threat was low. Based on experience of XVIII Airborne Corps medical personnel, compliance in combat units was well over 99% at the start of hostilities in January 1991. Dur-

ing this time there was a generally accepted perception of a definite nerve agent threat from chemically armed missiles. Again in February 1991, units entering Iraq and Kuwait at the start of ground combat perceived a real nerve agent threat, and there was virtually complete compliance with pyridostigmine dosing as ordered.

Most soldiers were aware that pyridostigmine altered their normal physiology in some way, but these changes did not interfere with their daily lives. This awareness was shared by medical personnel, including the authors of this report, who took pyridostigmine under field conditions. One percent of this military population had effects from pyridostigmine for which they sought medical advice. Fewer than 0.1% had effects sufficient to warrant discontinuation of the drug.

The most common side effects were related to the gastrointestinal and urinary tracts. These were predictable effects of muscarinic receptor activation. The worsening of symptoms in soldiers with acute bronchitis may have been the result of muscarinic activation of bronchial smooth-muscle receptors. The fact that few cases of asthma were exacerbated or unmasked may be due to this corps' deployment in the desert for about 4 months, so that those with asthmatic reactions had already been medically evacuated from the region.

The two episodes of hypersensitivity were not unexpected. Pyridostigmine is formulated as a bromide salt, and the bromide constituent has been implicated in rashes. The three incidents of slurred speech were unusual. Findings on neurological examinations were normal, and there was not excessive salivation. It is not known if there was oral or peripheral edema.

The bad dreams and equilibrium problems reported may have been stress responses, as they were not expected consequences of pyridostigmine administration. One advantage of pyridostigmine as a pretreatment for nerve agent poisoning is that it does not readily penetrate the blood-brain barrier or interfere with cognitive or psychomotor function.[6,7] Whether these individuals would have a recurrence of such symptoms if challenged with pyridostigmine under peacetime conditions is unknown.

Headaches were an unexpected phenomenon, and while only three soldiers sought medical attention for headaches, conversation with hospital personnel indicated that headaches were not rare occurrences. Two individuals assigned to a field hospital did not seek medical attention for headaches but reported that their blood pressures were moderately elevated during the episodes. The basis for the headaches may be that excess acetylcholine activated vascular receptors to induce vasodilation. This observation deserves further study.

The two episodes of hypertension were unexpected and may have represented a more prevalent phenomenon. The hypertension may have been due to hypersensitive sympathetic ganglionic receptors, subclinical pheochromocytoma, or other unknown mechanisms.

The signs and symptoms of pyridostigmine overdose, as described in military training literature, include abdominal cramps, nausea, diarrhea, pinpoint pupils, and muscular weakness, cramps, and twitching.[1] Abdominal cramps, nausea, and mild diarrhea were all experienced by soldiers receiving the prescribed dosage, as were rhinorrhea, flatulence, urinary urgency, and diaphoresis. Whether these were a consequence of dosage cannot be determined. Muscular weakness, cramps, and twitching were seen only in small women.

The pyridostigmine regimen followed by soldiers under wartime conditions caused a higher incidence of adverse physiologic events than had been reported in earlier peacetime evaluations. It seems possible that the combined stresses of anticipated combat, sleep deprivation, and life in the field may well have affected or modified many of these responses. Based on our observations, we conclude that the pyridostigmine regimen can be administered to virtually all soldiers under wartime conditions without impairment of military performance.

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